

PATENT COOPERATION TREATY

DV (M)

From the INTERNATIONAL SEARCHING AUTHORITY

To: ANN M. MUETING
MUETING, RAASCH, & GEBHARDT, P.A.
P.O. BOX 581415
MINNEAPOLIS, MN 55458-1415

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 284.00010201	Date of Mailing (day/month/year) 25 JAN 2001
International application No. PCT/US00/25482	International filing date (day/month/year) 25 AUGUST 2000
Applicant SKUBITZ, KEITH M.	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

RECEIVED

FEB 01 2001

MUETING AND RAASCH

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following.

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer MARIANNE P. ALLEN
Facsimile No. (703) 305-5230	Telephone No. (703) 308-0196

JOYCE BRIDGERS
PARALEGAL SPECIALIST
CHEMICAL MATRIX

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 284.00010201	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US00/23482	International filing date (day/month/year) 25 AUGUST 2000	(Earliest) Priority Date (day/month/year) 26 AUGUST 1999
Applicant SKUBITZ, KEITH M.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of _____ sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☒ Unity of invention is lacking (See Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/25482**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-10 for SEQ ID NO: 14

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

/USoo/23482

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/04, 38/17, 39/00; C07K 7/00, 7/08, 14/435, 17/00

US CL : 530/327, 350; 424/184.1, 185.1, 277.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/327, 350; 424/184.1, 185.1, 277.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG (files 5 and 155) and EAST (files U.S. patents, European abstracts, Japanese abstracts, and Derwent) search terms: CEACAM, BGP, biliary glycoprotein, CD66, CD66a, antigen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P ----- Y, P	US 5,965,710 A (BODMER et al) 12 October 1999, SEQ ID NO: 32.	1, 4-7 ----- 8-10
X ---- Y	US 5,571,710 A (BARNETT et al) 05 November 1996, abstract, claims, and columns 26-30.	1, 4-7 ----- 8-10
Y, P ----- A, P	SKUBITZ et al. Stimulation of Neutrophil Adhesion to Endothelial Cells by Synthetic Peptides of CD66a. Molecular Biology of the Cell. November 1999, Vol. 10, supplemental, abstract 452 on page 78A.	1, 4-10 ----- 2-3

☒ Further documents are listed in the continuation of Box C
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 05 JANUARY 2001	Date of mailing of the international search report 25 JAN 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer: <i>Joyce Bridges</i> MARIANNE P. ALLEN JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
/US00/23482

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	SKUBITZ et al. Synthetic Peptides of CD66a Stimulate Neutrophil Adhesion to Endothelial Cells. Journal of Immunology. 15 April 2000, Vol. 164, No. 8, pages 4257-64, especially abstract and Table I.	1-10
X	TEIXEIRA et al. The N-Domain of the Biliary Glycoprotein (BGP) Adhesion Molecule Mediates Homotypic Binding: Domain Interactions and Epitope Analysis of BGPC. Blood. 01 July 1994, Vol. 84, No. 1, pages 211-219, especially abstract and Figure 2.	1, 4-7
Y		8-10

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

- Group I, claims 1-10, drawn to a first set of peptides.
- Group II, claims 11-32, drawn to methods of activating or blocking activation of neutrophils.
- Group III, claims 19-26 and 32, drawn to methods of modulating and altering modulation of adhesion.
- Group IV, claims 27-32, drawn to methods of modulating immune cell activation, proliferation, or differentiation.
- Group V, claims 33-35, drawn to methods of delivering therapeutics.
- Group VI, claim 36, drawn to a method of modifying metastasis.
- Group VII, claim 37, drawn to a method of altering bacterial or viral binding to a biomaterial.
- Group VIII, claim 38, drawn to a method of altering cell adhesion to a biomaterial.
- Group IX, claim 39, drawn to a method of detecting tumors.
- Group X, claim 40, drawn to a method of detecting inflammation.
- Group XI, claim 41, drawn to a method of detecting a CD66 protein or ligand.
- Group XII, claim 42, drawn to a method of altering angiogenesis.
- Group XIII, claim 43, drawn to a method of altering immune response.
- Group XIV, claim 44, drawn to a method of altering keratinocyte proliferation.
- Group XV, claim 45, drawn to a second set of peptides.

It is noted that claim 32 appears in each of Groups II-IV. This claim is specifically directed to the three different methods of Groups II-IV and will be examined only to the degree that it reflects the elected invention and sequence (see below).

Sequence Election Requirement Applicable to All Groups

In addition, each Group detailed above reads on patentably distinct SEQ ID Numbers. Each sequence is patentably distinct because they are unrelated sequences, and a further restriction is applied to each Group. Applicant must further elect a single SEQ ID Number for an amino acid sequence. Each additional amino acid sequence is considered to be an additional group.

The inventions listed as Groups I-XV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Each of the products of Groups I and XV can be shown to be distinct, each from every other, as their structures differ. In addition, the set of peptides in Groups I and XV appear to be mutually exclusive. Thus, none share a special technical feature. Each of the methods of groups II-XIV do not require each other for their ultimate use and each method has different starting materials, method steps, and/or goals. Thus, they do not share a special technical feature. It is noted that not all of the products are used in each of the methods.

The examiner will rejoin claims directed to the first appearing method using the elected product to preserve unity of invention. Note that PCT Rule 13 does not provide for multiple products or multiple methods.

NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language ?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed ?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase ?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where and to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be couched with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/23482

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/04, 38/17, 39/00; C07K 7/00, 7/08, 14/435, 17/00
US CL : 550/327, 350; 424/184.1, 185.1, 277.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 550/327, 350; 424/184.1, 185.1, 277.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG (files 5 and 155) and EAST (files U.S. patents, European abstracts, Japanese abstracts, and Derwent) search terms: CEACAM, BGP, biliary glycoprotein, CD68, CD66a, antigen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y, P ----- A, P	SKUBITZ et al. Stimulation of Neutrophil Adhesion to Endothelial Cells by Synthetic Peptides of CD66a. Molecular Biology of the Cell. November 1999, Vol. 10, supplemental, abstract 452 on page 78A.	1, 4-10 ----- 2-3

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A		document defining the general state of the art which is not considered to be of particular relevance
* E	* X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* L	* Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* O		document referring to an oral disclosure, use, exhibition or other means
* P	* Z	document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

03 JANUARY 2001

Date of mailing of the international search report

25 JAN 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

MARIANNE P. ALLEN

Telephone No (703) 308-0196

JOYCE BRIDGERS
PARALEGAL SPECIALIST
CHEMICAL MATRIX

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/25482

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/23482

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-10 for SEQ ID NO: 14

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/23482

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-10, drawn to a first set of peptides.

Group II, claims 11-32, drawn to methods of activating or blocking activation of neutrophils.

Group III, claims 19-26 and 32, drawn to methods of modulating and altering modulation of adhesion.

Group IV, claims 27-32, drawn to methods of modulating immune cell activation, proliferation, or differentiation.

Group V, claims 33-35, drawn to methods of delivering therapeutics.

Group VI, claim 36, drawn to a method of modifying metastasis.

Group VII, claim 37, drawn to a method of altering bacterial or viral binding to a biomaterial.

Group VIII, claim 38, drawn to a method of altering cell adhesion to a biomaterial.

Group IX, claim 39, drawn to a method of detecting tumors.

Group X, claim 40, drawn to a method of detecting inflammation.

Group XI, claim 41, drawn to a method of detecting a CD66 protein or ligand.

Group XII, claim 42, drawn to a method of altering angiogenesis.

Group XIII, claim 43, drawn to a method of altering immune response.

Group XIV, claim 44, drawn to a method of altering keratinocyte proliferation.

Group XV, claim 45, drawn to a second set of peptides.

It is noted that claim 32 appears in each of Groups II-IV. This claim is specifically directed to the three different methods of Groups II-IV and will be examined only to the degree that it reflects the elected invention and sequence (see below).

Sequence Election Requirement Applicable to All Groups

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The inventions listed as Groups I-XV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Each of the products of Groups I and XV can be shown to be distinct, each from every other, as their structures differ. In addition, the set of peptides in Groups I and XV appear to be mutually exclusive. Thus, none share a special technical feature. Each of the methods of groups II-XIV do not require each other for their ultimate use and each method has different starting materials, method steps, and/or goals. Thus, they do not share a special technical feature. It is noted that not all of the products are used in each of the methods.

The examiner will rejoin claims directed to the first appearing method using the elected product to preserve unity of invention. Note that PCT Rule 13 does not provide for multiple products or multiple methods.

PATENT COOPERATION TREATY

PCT

REC'D 13 MAY 2002



IPC

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

10/069040

Applicant's or agent's file reference 6072.204-WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK01/00020	International filing date (day/month/year) 12/01/2001	Priority date (day/month/year) 12/01/2000
International Patent Classification (IPC) or national classification and IPC C12N9/44		
Applicant NOVOZYMES A/S et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items.</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the reportII <input type="checkbox"/> PriorityIII <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input checked="" type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input type="checkbox"/> Certain documents citedVII <input type="checkbox"/> Certain defects in the international applicationVIII <input type="checkbox"/> Certain observations on the international application		
Date of submission of the demand 21/05/2001	Date of completion of this report 08.05.2002	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Seranski, P Telephone No +49 89 2399 7846 	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK01/00020

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*)
Description, pages:

1-146 as originally filed

Claims, No.:

1- 59 as originally filed

Drawings, sheets:

1/1 as originally filed

Sequence listing part of the description, pages:

1-35, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/DK01/00020

listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 23-59.

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 23-59.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/DK01/00020

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:
 - ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
 - ☐ complied with.
 - ☐ not complied with for the following reasons:
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
 - ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-22.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-22
	No: Claims
Inventive step (IS)	Yes: Claims
	No: Claims 1-22
Industrial applicability (IA)	Yes: Claims
	No: Claims 1-22

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/DK01/00020

Re Item I

Basis of the report

1. Claims 48-58 have been filed during the Search Phase of the International Application. No search has been carried out on said claims and in consequence, no examination will be carried out on claims 48-58.

Re Item IV

Lack of unity of invention

2. Reference is made to the following documents:

- D1: DATABASE STN INTERNATIONAL [Online] CAPLUS, CAPLUS accession no. 1999:702733; document no. 132:31329, YAMASHITA, MITSUO: 'Monograph: Studies on the improvement of functions useful proteins' XP002901781 & SEIBUTSU KOGAKU KAISHA, vol. 77, no. 8, 1999, pages 345-357,
- D2: MITSUO YAMASHITA ET AL: 'Random Mutagenesis of pullulanase from Klebsiella aerogenes for studies of the structure and function of the enzyme' J. BIOCHEM, vol. 116, 1994, pages 1233-1240, XP002901782
- D3: MICHAEL J. MCPHERSON: 'Functional analysis of the starch debranching enzyme pullulanase' BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 16, 1988, pages 723-724, XP002901783
- D4: DATABASE STN INTERNATIONAL [Online] Medline, Medline accession no. 9879259; KATSUYA Y ET AL: 'Three-dimensional structure of pseudomonas isoamylase at 2.2 Å resolution' XP002901784 & JOURNAL OF MOLECULAR BIOLOGY, 4 September 1998 (1998-09-04), pages 885-897, England
- D5: WO 98 38287 A (NOVO NORDISK AS) 3 September 1998 (1998-09-03)

2.1 The Examining Authority agrees with the finding of the International Search Authority for Lack of Unity of the present Application following Rule 13.1 and 13.2 PCT.

It is considered that at least four different inventions are claimed for in this application, that are not linked by a common novel and inventive concept.

2.2 Prior art already teaches variants of pullulanases (see documents D1 and D2). Prior art further teaches to design enzyme variants with altered properties by determining the three-dimensional structure of the enzyme and with the knowledge of this structure designing enzyme variants. The structure function relationship of pullulanase has been analysed.

2.3 The inventions found in the present application are:

I) Claims 1-22

Methods for producing a variant of a parent pullulanase.

II) Claims 23, 28, 33-37, 40 and part of claims 26, 27, 31, 32, 39, 41-47 and 59

Pullulanase variants having improved thermostability compared to the parent pullulanase.

III) Claims 24, 29, 38 and part of claims 26, 27, 31, 32, 41-47 and 59

Pullulanase variants having increased isoamylase activity

IV) Claims 25, 30 and part of claims 26, 27, 31, 32, 39, 41, 42, 44-47 and 59

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. Inventive Step (Art.33(3) PCT

3.1 Present claims 1-22 concern methods of producing variants of pullulanase, wherein said methods are based on the determination of the three-dimensional structure of an already known pullulanase, namely 'Promozym'. Said methods are further related to the modification of said pullulanase using site directed mutagenesis to enhance the properties of said pullulanase as set out in dependent claim 2.

3.2 Document D1 recites a review that discloses in particular the possibility of structure-function analysis in enzymes using the three-dimensional structure of said enzymes. The review suggests that said structure determination helps to alter the specific activity, substrate specificity and optimum pH of enzymes, increase the thermal stability of proteins and to design proteins that can be used in nonaqueous solvents. Moreover, D1 specifically discloses an example of the analysis of the structure-function relationship of pullulanase and the engineering of starch-processing enzymes by recombinant DNA technology.

3.3 Document D2 discloses the alteration of the catalytic activity of pullulanase with regard to its thermal stability. Said alterations were achieved by performing random mutagenesis and subsequent functional analysis. Certain changes in the amino acid sequence of pullulanase were disclosed that are related to thermal stability (e.g. Table 1, Fig.1-3).

3.4 Document D3 discloses an analysis of structure-function relationship of pullulanase. It suggests that certain conserved regions in the enzyme include residues implicated in substrate binding and catalysis. It further suggests some degree of functional and mechanistic similarity between pullulanase and alpha-amylase.

3.5 Document D4 discloses the three dimensional-structure of an isoamylase from *Pseudomonas amyloclavata*, which hydrolyses alpha-1,6-glucosidic linkages of amylopectin and glycogen.

3.6 Document D5 is a similar application of the same applicant disclosing the three-dimensional structure of laccase mutants. D5 discloses the same procedure that has been used in the present application that is determining the three-dimensional structure of an enzyme and using this structure information to start with directed mutagenesis to alter the characteristics of the enzyme.

4. For the assessment of inventive step, document D2 is regarded as to represent the closest prior art. The difference of the methods of claims 1-22 of the present application to the methods disclosed in D2 is that in the present application the three-dimensional structure of the pullulanase has been determined prior to the mutagenesis of the amino acid sequence. However, the application does not provide a single example that this

method leads to a different alteration of the pullulanase compared to that disclosed in D2. The objective technical problem that has been solved by the present application can therefore be formulated as to provide an alternative method for the alteration of pullulanase. This problem has been solved by determining the three dimensional structure of pullulanase and using the structure information for directed mutagenesis.

4.1 This is not interpreted as to involve any inventive skill. The present application used the three dimensional structure of an already known and commercially available enzyme. Furthermore, the skilled person was aware from the disclosure in D1 and D4 that three-dimensional structure determination facilitates the analysis of structure-function relationship of particularly pullulanase and in a further aspect, certain regions in the pullulanase primary structure that are suitable for alterations have already been disclosed in D3 and the skilled person had a clear guidance how to come from a resolved three-dimensional structure of an enzyme to a site directed mutagenesis of said enzyme by the disclosure of document D5.

4.2 Consequently the methods of claims 1-22 lack an inventive step as required by Art.33(3) PCT.

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

10

Applicant's or agent's file reference FU 218-P WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT IPEA 416)	
International application No. PCT/CH00/00076	International filing date (day month year) 10 February 2000 (10.02.00)	Priority date (day month year) 08 April 1999 (08.04.99)	
International Patent Classification (IPC) or national classification and IPC A23N 17:00			
Applicant BÜHLER AG			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.



This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 16 August 2000 (16.08.00)	Date of completion of this report 14 May 2001 (14.05.2001)
Name and mailing address of the IPEA EP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No

PCT CH00 00076

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

- ☐ the international application as originally filed.
- ☒ the description, pages 1,3-5, as originally filed.
 pages _____, filed with the demand,
 pages 2,2a, filed with the letter of 09 February 2001 (09.02.2001),
 pages _____, filed with the letter of _____.
- ☒ the claims, Nos. _____, as originally filed,
 Nos. _____, as amended under Article 19,
 Nos. _____, filed with the demand,
 Nos. 1-6, filed with the letter of 09 February 2001 (09.02.2001),
 Nos. _____, filed with the letter of _____.
- ☒ the drawings, sheets/fig 1/1, as originally filed,
 sheets/fig _____, filed with the demand,
 sheets/fig _____, filed with the letter of _____,
 sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/CH 88/000076

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-6	YES
	Claims		NO
Inventive step (IS)	Claims	1-6	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-6	YES
	Claims		NO

2. Citations and explanations

1. The subject matter of independent Claims 1 and 5 can be considered novel, inventive and industrially applicable and thus fulfils the requirements of PCT Article 33. The cited prior art does not disclose or suggest any apparatus or process wherein flour or a similar bulk commodity is heated in a heated batch mixer, then dried and cooled in batches before being mixed with additives in the second batch mixer. JP 08 009 893 (abstract) and SU 697 127 (abstract) describe processes which, for example, cannot be implemented batchwise and, even in conjunction with IE-A-930995, do not lead to the claimed subject matter, since the apparatus described therein does not make possible the steps of the claimed process (thermal treatment - drying/cooling addition of additives), because conditioning, expanding, pelleting and cooling take place after the addition of additives.
2. Claims 2 to 4 and 6 are dependent on Claims 1 and 5 respectively and thus likewise satisfy the requirements of the PCT with regard to novelty, inventive step and industrial applicability.

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/FR01/00764	International filing date (day/month/year) 15 March 2001 (15.03.01)	Priority date (day/month/year) 16 March 2000 (16.03.00)
International Patent Classification (IPC) or national classification and IPC C07D 409/12		
Applicant SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)		

<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>2</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u> </u> sheets.</p>
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input checked="" type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>

Date of submission of the demand 19 September 2001 (19.09.01)	Date of completion of this report 15 June 2002 (15.06.2002)
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No PCT/FR01/00764

I. Basis of the report

The basis of international preliminary examination report is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims corresponding to inventions or groups of inventions for which additional search fees may have not been paid, and consequently may have not been searched (Article 17(3)(a) and Rule 66.1(e) PCT; see also international search report).

IV. Lack of unity of invention

The objection as to lack of unity raised in the international search report is maintained.
The reasons for the objection are the same as those indicated in the international search report.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 27 September 2001 (27.09.01)	
International application No. PCT/US00/23482	Applicant's or agent's file reference 284.00010201
International filing date (day/month/year) 25 August 2000 (25.08.00)	Priority date (day/month/year) 26 August 1999 (26.08.99)
Applicant SKUBITZ, Keith, M. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
26 March 2001 (26.03.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Henrik NYBERG Telephone No.: (41-22) 338.83.38
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